CRP and Calprotectin

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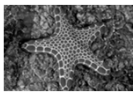
Faculty Disclosure

- **Faculty:** Karen Kroeker
- **Relationships with commercial interests:**
  - **Grants/Research Support:** FLIBD
  - **Speakers Bureau/Honoraria:** Abbvie, Warner Chilcott, Shire
  - **Consulting Fees:** Baxter, Janssen Canada, Ferring, Shire
  - **Other:** None

Objectives



1. Understand the role of biomarkers in the diagnosis and management of patients with IBD
2. Discuss CRP – what does it mean?
3. Describe calprotectin in assessing active GI disease

TRIVIA: What do CRP & Sea stars have in common?

Biomarkers & IBD

- Currently, there is no "gold standard" test for IBD
- A good biomarker would help us be **more objective** in our assessment (cf assessment of symptoms which are subjective) and **less invasive** than endoscopy
- A good biomarker is:
  1. Easy and rapid to perform (minimally invasive)
  2. Cheap
  3. Reproducible (b/w pts and labs)
- CRP & Fecal Calprotectin are 2 biomarkers used in IBD

Gut 2006;55:426–431

C-REACTIVE PROTEIN

What is CRP?

- Acute phase protein, sensitive marker of inflammation
  - Named for its capacity to precipitate the somatic C-polysaccharide of *Streptococcus pneumoniae*
- Produced by hepatocytes, primarily under the control of IL-6
- Half-life ~19 hours
  - Rises quickly within 6 hours, peaks at 48 hours
- CRP gene (chr. 1), has many polymorphisms, may account for baseline variation

J. Clin. Invest. **111**:1805–1812 (2003), Gut 2006;55:426–431

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Understanding CRP

- Non-specific marker of inflammation
  - Few drugs reduce CRP unless they also affect the underlying pathology causing the increased CRP
- The hs-CRP (used in CV disease) is not a different molecule; it just means the assay has a lower limit of detection
- BMI is associated with baseline CRP
  - Weight loss lowers CRP
  - Raised baseline CRP is associated with insulin resistance or metabolic syndrome
  - Adipocytes are the source of most of baseline IL-6

J. Clin. Invest. **111**:1805–1812 (2003).

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Acute Phase Reactants

Table 1
Changes in concentrations of plasma proteins in the acute-phase response

	Increased	Decreased
Proteinase inhibitors	α_1-Antitrypsin	Inter-α-antitrypsin
	α_1-Antichymotrypsin	
Coagulation proteins	Fibrinogen	
	Prothrombin	
	Factor VIII	
	Plasminogen	
Complement proteins	C1s	Properdin
	C2	
	B	
	C3	
	C4	
	C5	
	C1 inhibitor	
Transport proteins	Haptoglobin	
	Hemopexin	
	Ceruloplasmin	
Miscellaneous	CRP	Albumin
	SAA	Transthyretin
	Fibronectin	HDL
	α_1-acid glycoprotein	LDL
	Gc globulin	

J. Clin. Invest. **111**:1805–1812 (2003).

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CRP Diseases

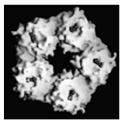

Table 2
CRP responses in disease

Major CRP acute-phase response	
Infections	Bacterial
	Systemic/Severe fungal, mycobacterial, viral
Allergic complications of infection	Rheumatic fever
	Erythema nodosum
Inflammatory disease	Rheumatoid arthritis
	Juvenile chronic arthritis
	Ankylosing spondylitis
	Psoriatic arthritis
	Systemic vasculitis
	Polymyalgia rheumatica
	Reiter disease
	Crohn disease
	Familial Mediterranean fever
Necrosis	Myocardial infarction
	Tumor embolization
	Acute pancreatitis
Trauma	Surgery
	Burns
	Fractures
Malignancy	Lymphoma
	Carcinoma
	Sarcoma
Modest or absent CRP acute-phase response	
	Systemic lupus erythematosus
	Scleroderma
	Dermatomyositis
	Ulcerative colitis
	Leukemia
	Graft-versus-host disease

J. Clin. Invest. **111**:1805–1812 (2003).

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CRP & IBD

- Elevated CRP is associated with symptoms and endoscopic active disease for both CD & UC
- Cut-offs have been suggested (mild: 10-50; moderate: 50-80, severe: >80 mg/l), but it is more important to compare with pt's previous levels
- Elevated CRP can predict risk of surgery (Oxford Rule)
- Elevated CRP predicts response to anti-TNF therapy

Inflamm Bowel Dis 2005;11:707–712. Gut 2006;55:426–431

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CALPROTECTIN

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What is Calprotectin?

- 1st described in 1980
- Calcium and zinc binding protein found in the cytosol of neutrophils (and macrophages)
- Found in plasma, urine, CSF, feces, saliva, etc.
- Is a DAMP protein (damage associated molecular pattern); released by the innate immune system by damaged or activated cells
- Fecal calprotectin is raised in any GI inflammatory process, including IBD

World J Gastroenterol 2012 December 14; 18(46): 6782-6789

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Uses for Fecal Calprotectin

- Distinguish IBD vs. IBS
- Distinguish active and quiescent disease in IBD
- Assessing response to treatment of IBD
- Predict relapse in patients with IBD

World J Gastroenterol 2012 December 14; 18(46): 6782-6789

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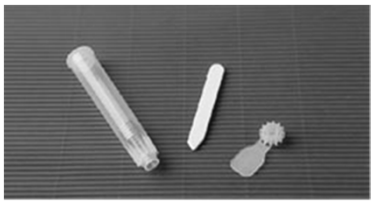
Collecting Fecal Calprotectin



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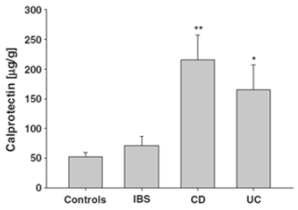
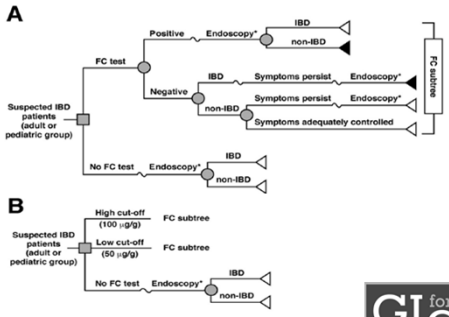
Fecal Calprotectin Can Distinguish IBD from Controls & IBS



Journal of Crohn's and Colitis (2012) 6, 207–214

Calprotectin – ?Algorithm for IBD



Clin Gastro Hep 2014 epub

Calprotectin – ?Algorithm for IBD

- US Study – Effectiveness & Cost-Effectiveness
- FC saved $400/pt but delayed diagnosis in 7%
- Cost-effectiveness depended on the pre-test probabilities
  - If pre-test prob <75% → cost-effective
  - If pre-test prob >85% → not cost-effective
- Using a lower FC cut-off (50 v. 100 ng/mL) → improved accuracy in diagnosis 95% v. 87% (not including delated Dx, but cost an additional $55/pt

Clin Gastro Hep 2014 epub

Fecal Calprotectin in UC

- Correlation of non-invasive markers with endoscopic activity in UC
- FC (r=0.821) was the best, Lichtiger Index (r=0.682), CRP (r =0.556), platelets (r=0.488), WBC(r=0.401), and hemoglobin (r=-0.388)
- Only fecal calprotectin was able to discriminate between grades of endoscopic severity
  - grade 0, 16 [10–30]mg/g (normal)
  - grade 1, 35 [25–48] mg/g (granular, loss of vasc pattern)
  - grade 2, 102 [44–159] mg/g (friable, but not spontaneous bleeding)
  - grade 3, 235 [176–319] mg/g (microulcerations, spont. Bleeding)
  - grade 4, 611 [406–868] mg/g (gross ulcerations, denuded mucosa)

Inflamm Bowel Dis 2013;19:332–341

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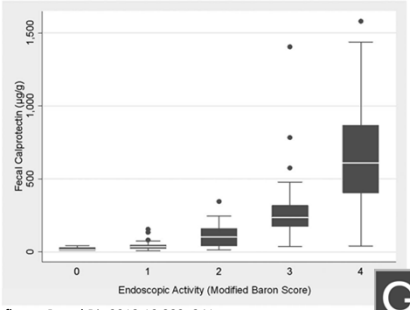
FC & Endoscopic Activity



Inflamm Bowel Dis 2013;19:332–341

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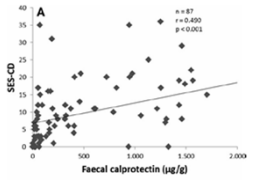
Fecal Calprotectin in CD

- Fecal calprotectin can predict disease severity in Crohn's disease, but with lower sensitivity and specificity than UC
- It is better in colonic than ileal disease
- Fecal calprotectin was just as good as CRP + fecal calprotectin



Inflamm Bowel Dis 2012;18:2218–2224

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Summary

- Biomarkers, like CRP and fecal calprotectin are non-invasive markers that are helpful in the management of IBD
- CRP

  - Advantages
    - Readily available
  - Disadvantages
    - Not everyone makes CRP, not-specific for the gut

TRIVIA Answer: Pentaradial symmetry

Summary (2)

- Fecal Calprotectin
  - Advantages:
    - More specific for intestinal inflammation
    - Quick
    - Less invasive
  - Disadvantages:
    - Not readily available (yet)
    - Requires a stool sample (patients don't often like this

QUESTIONS?